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## DISORDERS OF CALCIUM METABOLISM

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Key words: calcium, phosphorus, parathyroid hormone, vitamin D, calcitonin, hypercalcemia, hypocalcemia, hyperparathyroidism

### Objectives

- A. Describe the GI and renal handling of calcium and phosphorus
- B. Describe the secretion and actions of parathyroid hormone, vitamin D, and calcitonin
- C. Describe the pathophysiology and clinical abnormalities which occur in patients with hyperparathyroidism and hypoparathyroidism
- D. Describe the pathophysiology and clinical abnormalities which occur in patients with vitamin D excess and vitamin D deficiency

### I. Calcium, phosphorus metabolism

#### A. Calcium

- 1. The major element of the skeleton provides major mechanical function. Approximately 1000 gm in skeleton.
- 2. ECF Calcium about 1 gm
- 3. Calcium is a critical ion for normal neuromuscular function, enzyme action, blood coagulation, membrane function and hormonal secretion.
- 4. Calcium in serum
  - a. Regulated within narrow limits; approx. 9.0-10.5 mg/dl
  - b. Less than 50% is ionized. Majority of the rest is bound to albumin. Rule of thumb: 0.8 mg/dl Ca change for each 1 gm/dl change in albumin.
  - c. Calcium and phosphate in serum are nearly saturated.
  - d. Ionization decreases in alkaline pH
- 5. G.I. Absorption
  - a. Average 1 gm intake but only 10 to 20%, absorbed - net.
  - b. Absorption is an active process which is vitamin D dependent.
- 6. Renal excretion
  - a. 99% of filtered  $\text{Ca}^{++}$  is reabsorbed.
  - b. Reabsorption occurs in the proximal tubule linked to sodium reabsorption.
  - c. Reabsorption in the distal tubule is Pth dependent.

#### B. Phosphorus

- 1. Present in skeleton as hydroxyapatite and widely distributed in macromolecules.
- 2. Normal serum levels 3.0-4.5 mg/dl in adults. Solubility product with calcium means that changes in Ca or  $\text{PO}_4$  result in reciprocal changes in the other.
- 3. G.I. absorption is efficient, primarily in duodenum and jejunum. Absorption is increased by vitamin D.
- 4. Renal excretion is regulated by Pth.

### II. Hormonal control

A. Parathyroid hormone

1. Regulation of secretion
  - a. Major factor is plasma level of ionized calcium.
  - b. Parathyroid chief cells sense  $\text{Ca}^{++}$  via a cell membrane bound calcium receptor.
  - c. 1,25-dihydroxycholecalciferol decreases secretory responses to hypocalcemia.
  - d. Hyperphosphatemia is a weak stimulus of secretion.
2. Actions
  - a. Kidney
    - i. Increased phosphate excretion: Decrease proximal tubular reabsorption of phosphate ion. This is the major effect.
    - ii. Effect on phosphate is mediated through internalization of membrane bound sodium-phosphate cotransporters.
    - iii. Increases calcium reabsorption in the distal tubule
    - iv. Effects are mediated through cAMP.
    - v. Stimulates 1-alpha hydroxylation of 25-hydroxy cholecalciferol
  - b. Bone
    - i. Increases osteocytic and osteoclastic osteolysis, leads to increased release of  $\text{Ca}^{++}$  and  $\text{PO}_4$ .
    - ii. Probably plays a role in bone remodeling.
  - c. Gut - Promote absorption of Ca and  $\text{PO}_4$  by increasing vitamin D production.

B. Vitamin D

1. Structure and metabolism



1,25 dihydroxy D is the active metabolite.

2. Sources
  - a. 7-dehydrocholesterol stored in skin in large amounts.
  - b. Vitamin D added to milk, cereal, etc.
3. Regulation of vitamin D metabolism
  - a.  $1\alpha$ -hydroxylase is the regulated step
  - b. Pth and hypophosphatemia both increase  $1\alpha$ -hydroxylase activity
  - c. 1,25 dihydroxy D inhibits activity
4. Actions
  - a. Gut - stimulate calcium (primary effect) and phosphate absorption
  - b. Parathyroid - suppress PTH synthesis and secretion
  - c. Bone - in higher doses, stimulate resorption. Allows effect of Pth.

C. Calcitonin

1. 32 amino acid peptide produced in the C cells of the thyroid.
2. Inhibits osteoclastic activity.

3. No known disorders of calcium metabolism relate to alterations in calcitonin secretion.
4. Elevated calcitonin levels are an important marker for medullary carcinoma of the thyroid.
5. Calcitonin is used therapeutically in hypercalcemia, Paget's disease, and osteoporosis.

### III. Primary hyperparathyroidism

A 55 year old man was admitted to the hospital with excruciating left flank pain of two hours duration. He also gave a history of two years of increasing anorexia, nausea, constipation, and a 15 pound weight loss. He complained of increased fatigue and weakness, and had suffered intermittent rib pain for the past five months.

On physical examination, blood pressure was 150/105, pulse 85 and temperature 37°C. He was obviously very uncomfortable, and had marked tenderness in the left costovertebral angle, the left flank, and left lower quadrant of the abdomen. The rest of the exam was negative.

On urinalysis, he had 20-30 RBC and 2-5 WBC per hi power; Serum Ca = 14.2 mg/dl (8.5-10.5); PO4 = 1.7 mg/dl (3.0-4.5); Alkaline phosphatase = 205 units/ml (nl 100). Chest film showed decreased bone mineralization, and CT demonstrated a left ureteral stone.

He was treated with narcotics and bed rest, and on the third hospital day he spontaneously passed a calcium oxalate stone. Subsequent evaluation showed a 24 hour urine calcium of 348 mg/24<sup>h</sup> (150-250) and a serum parathyroid hormone level of 123 pg/ml (10-65).

One month later he underwent neck exploration, and a 1 x 1 cm parathyroid adenoma was removed. Postoperatively, serum calcium fell to 7.6 mg/dl and he had symptoms of tetany. He was treated with calcium infusions, and by ten days post op his calcium was 8.4 mg/dl. Two weeks after discharge his calcium was 8.9 mg/dl and he felt better than he had during the past two to three years.

- A. Syndrome is a result of excessive secretion of parathyroid hormone.
  1. Common disorder occurs more commonly in women. Increased incidence among older individuals.
  2. Most commonly due to a single benign adenoma. Less often due to hyperplasia. When part of an MEN syndrome, is always hyperplasia.
- B. Clinical manifestations
  1. Most people are asymptomatic
  2. Renal - kidney stones, hyposthenuria, renal failure
  3. Bone - pain, pathologic fractures
  4. GI - anorexia, nausea, vomiting, constipation
  5. Neurologic - lethargy, weakness, tremor
- C. Laboratory abnormalities
  1. Increased serum calcium
  2. Decreased serum phosphate
  3. Increased alkaline phosphatase
  4. Increased urinary calcium
  5. Increased serum parathyroid hormone
- D. Diagnosis
  1. Increased serum calcium
  2. Elevated PTH levels
  3. Urinary calcium level to exclude Familial Hypocalciuric Hypercalcemia
- E. Therapy
  1. Parathyroidectomy for younger individuals and those with severe or symptomatic cases

2. Older asymptomatic patients may not need therapy
3. Cinacalcet (calcium receptor agonist) is effective, but only approved for patients with secondary hyperparathyroidism or parathyroid carcinoma

#### IV. Hypercalcemia of malignancy

##### A. Etiology & frequency

1. Common occurrence in many neoplasms, usually as a late manifestation of disease
2. Often due to overproduction of Pth related protein (PTHrP).
  - a. PTHrP has some homology with PTH, binds to PTH receptors, and mimics all known actions of PTH
  - b. Levels are commonly elevated in patients with squamous cell carcinoma of lung and head and neck. Many other tumors may also overproduce PTHrP.
  - c. PTHrP and PTH are measured separately. Both assays are specific.
3. Locally active cytokines mediate bone resorption.
  - a. Multiple myeloma and some lymphomas are most common.
  - b. Breast cancer may activate both local and systemic mechanisms.
4. Some lymphomas cause hypercalcemia by expressing large amounts of 1-alpha hydroxylase activity

##### B. Diagnosis is usually straightforward

##### C. Clinical manifestations

1. Because of the rapid onset, CNS and GI symptoms tend to predominate
2. With mild to moderate hypercalcemia, symptoms are similar to those of hyperparathyroidism
3. With severe hypercalcemia (>15 mg/dl) patients may develop obtundation, disorientation, coma.
4. Volume depletion is uniformly present

##### D. Treatment

1. Hydration with saline
2. Pamidronate, Zoledronic acid
3. Loop diuretics; only after hydration
4. Gallium nitrate
5. Calcitonin

#### V. Vitamin D Intoxication

A 64 year old philanthropist has had increasing nausea, vomiting, anorexia and constipation for 8 months. During the last 4 weeks his physicians have noticed lethargy, disorientation and decreasing mental status. His attending physicians have found the serum calcium to be elevated, and asked for consultation by an endocrinologist.

On physical exam, his blood pressure was 140/100, pulse was 84. He was disoriented and unable to give a coherent history. No bowel sounds were heard on abdominal examination. Neurologic exam showed markedly decreased mental status, but he could move all extremities and was responsive to pain. He was able to follow simple commands.

Ca = 16.4 mg/dl (8.5-10.5), PO<sub>4</sub> = 4.8 mg/dl (3.0-4.5), Albumin = 4.1 gm/ dl (3.5-4.5).

A brief survey of his medicine chest disclosed large amounts of vitamin preparations. He was treated with saline and glucocorticoids with rapid fall of his calcium to 11.4 mg/dl. He woke up within 36 hours, and his mental status returned to its usual alert state.

##### A. Excessive intake or production of vitamin D

1. Granulomatous diseases and some lymphomas
  2. Inadvertent overdosage in hypoparathyroidism
  3. Associated with megavitamin therapy
- B. Etiology and Pathogenesis
1. Granulomatous disease
    - a. Macrophages have  $\alpha$ -hydroxylase activity.
    - b. When there is a marked increase in macrophages, increased 1, 25 dihydroxy D is secreted.
  2. Exogenous overdose
    - a. Since 1,25-dihydroxycholecalciferol regulates its own synthesis, modest overdosage of vitamin D causes no abnormalities.
    - b. When massive doses are given, enough active vitamin D is generated to cause increased calcium absorption.
    - c. When 1,25 dihydroxy D is used in therapy, modest overdoses are much more likely to cause abnormalities.
  3. Pathophysiology
    - a. With moderate hyperabsorption of calcium, Pth levels are suppressed and hypercalciuria occurs, maintaining normal serum calcium.
    - b. With severe hyperabsorption, renal excretory capacity is exceeded, and hypercalcemia ensues.
- C. Symptoms are entirely due to hypercalcemia and hypercalciuria
1. Renal disease and stones
  2. GI symptoms
  3. CNS dysfunction
- D. Therapy
1. Treat granulomatous disease or remove vitamin D excess
  2. Saline infusion to enhance calcium excretion
  3. Glucocorticoids to antagonize effects of vitamin D

## VI. Hypoparathyroidism and Pseudohypoparathyroidism

A 21 year old woman was seen in neurology clinic for evaluation of a convulsive disorder. Despite taking phenytoin and phenobarbital she had continued to have convulsions several times a year for the past several years. In addition, she had intermittent muscle twitching.

On physical exam she had positive Chvostek and Trousseau signs. Her serum Ca = 7.2 mg/dl (8.5-10.5),  $PO_4 = 6.5$  mg/dl (3.0-4.5), Albumin = 4.1 gm/dl (3.5-4.5), BUN - 10 mg/dl (6-20), creat - 1.0 mg/dl (<1.2).  $72^\circ$  fecal fat measurement was less than 5 gm.

Serum parathyroid hormone level was 158 pg/ml (10-65).

She was treated with high dose vitamin D therapy and calcium tablets. Serum calcium was maintained in the 7.9-8.8 mg/dl range. Anticonvulsant medication was discontinued, and all symptoms abated.

- A. Decreased production or activity of Pth
- B. Symptoms: increased neuromuscular irritability, twitching, tetany, convulsions
- C. Laboratory abnormalities
  1. Low serum calcium
  2. High phosphate
  3. If hypoparathyroidism, serum Pth is low
  4. If pseudohypoparathyroidism (end organ resistance) serum Pth is high.

5. Basal ganglion calcification

D. Therapy: High dose calcium and vitamin D

## VII. Vitamin D Deficiency

A 47 year old man had resection of 15 feet of small intestine 10 years earlier for inflammatory bowel disease. He was admitted for evaluation of recurrent fractures; four in the past 18 months. Two of the fractures were not associated with any apparent trauma.

On physical exam he was 5'10", 124 lbs. He had generalized bone tenderness.

Ca = 8.6 mg/dl (8.5-10.5), PO<sub>4</sub> = 1.2 mg/dl (3.0-4.5), Albumin = 3.7 gm/dl (3.5-4.5), Hgb = 9.7 gm/dl (13-15), Carotene = 37 mg/dl (100-200), cholesterol = 107 gm/dl (160-250), Alkaline phosphatase = 382 (under 100).

A 72 hour fecal fat was 28 gm (under 5). Serum parathyroid hormone was 385 pg/ml (10-65). Serum 25 hydroxycholecalciferol levels were unmeasurable. Bone biopsy showed increased osteoid seams.

He was treated with high dose vitamin D and calcium tablets with some improvement in bone pain. No further fractures were seen over the following year.

### A. Etiology

1. Inadequate intake and sunlight
2. Malabsorption
3. Severe liver disease
4. Renal failure

### B. Pathogenesis

1. Vitamin D deficiency leads to decreased absorption of calcium by the GI tract.
2. As serum calcium starts to fall, secondary hyperparathyroidism occurs.
3. Elevated Pth levels may maintain serum calcium in the normal range, but at the cost of phosphaturia, hypophosphatemia and increased bone reabsorption
4. Low serum phosphate results in inadequate bone mineralization and osteopenia.
5. In severe cases, secondary hyperparathyroidism is not adequate to maintain serum calcium levels, and hypocalcemia occurs.

### C. Clinical Manifestations

1. Bone pain and pathologic fractures
2. Decreased bone density
3. Hypophosphatemia, increased alkaline phosphatase and increased Pth
4. Low urinary calcium levels
5. Late hypocalcemia

D. Therapy: vitamin D replacement; patients with renal failure need 1,25 dihydroxycholecalciferol

## VIII. Secondary hyperparathyroidism

A 35 year old diabetic man presented with chronic renal failure. He had weakness, anorexia, vomiting, dyspnea and pleuritic chest pain. He also complained of several months of diffuse bone pain.

BUN = 238 mg/dl (6-20), Creat = 14.4 mg/dl (1.2), Hgb = 5.1 gm/dl (13-15), Glucose 274 mg/dl, Ca = 6.0 mg/dl (8.5-10.5), PO<sub>4</sub> = 10.1 mg/dl (3.0-4.5), Albumin = 2.5 gm/dl (3.5-4.5), PTH 498 pg/ml (10-65).

Treatment was instituted with hemodialysis, phosphate binding agents and 1,25 dihydroxycholecalciferol.

A. Increased parathyroid secretion in response to decreased plasma calcium level

- B. Commonly occurs in renal failure and vitamin D deficiency
- C. Serum calcium may be low or normal, prolonged Pth secretion may result in bone resorption, bone pain and fracture.
- D. Treatment
  - 1. Treat underlying cause
  - 2. Phosphate binders for renal failure
  - 3. Calcitriol
  - 4. Paracalcitol
  - 5. Cinacalcet